DCB in CLI: rationale and benefit in current times

Vincenzo Foppa, 1462
“The miracle of the salvaged foot”
Cappella Portinari, S. Eustorgio Church
Milan, Italy
Disclosure

Roberto Ferraresi, MD

In the last 2 years I have the following potential conflicts of interest to report:

**Consultant:** Medtronic, Abbott, Boston Scientific, Contract Medical International, Cook, Asahi, Ivascular, Biotronik, Limflow, Spectranetics, Shire, Kardia, Astra Zeneca, Orbus, Bard, Philips, Volcano, Novena, Angiodroid, M&L Healthcare

**Virtual shareholder:** Limflow
- Fem-pop endovascular treatment
- 28 RCTs (24 DCB + 4 DES) vs. PTA
- N = 4663 pts → **89% IC, 11% CLI**
- Primary safety measure: all-cause death

Conclusions—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted.
Jan 17th

FDA recommends to:

1. Continue patient surveillance
2. Discuss risks/benefits of all PAD treatment options with your pts
3. Report adverse events or suspected adverse events

FDA believes that the benefits continue to outweigh the risks
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Mar 15th
FDA recommends to:
1. Consider alternative treatment options for most pts
2. For some pts at high risk of restenosis, clinicians may determine that the benefits may still outweigh risks
3. Ensure pts receive OMT for PAD

FDA replicated the analysis with patient-level data → preliminary results confirmed the presence of a signal

**FDA letters to Heath Care Providers - 2019**

**Jan 17th**
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**Aug 7th**
FDA recommends to:

1. When making treatment recommendations, and as part of the informed consent process, consider that there may be an increased rate of long-term mortality in pts treated with PCB and PES.
2. Discuss the risks and benefits of all available PAD treatment options with your pts. For many pts, alternative treatment options to PCB and PES provide a more favorable benefit-risk profile based on currently available information.
3. For individual pts judged to be at particularly high risk for restenosis and repeat fem-pop interventions, clinicians may determine that the benefits of using a paclitaxel-coated device outweigh the risk of late mortality.
4. In discussing treatment options, physicians should explore their pts’ expectations, concerns and treatment preferences.

**Jun 2019 Panel Meeting conclusion:**

“... a late mortality signal associated with the use of paclitaxel-coated devices to treat fem-pop PAD was present.

... the magnitude of the signal should be interpreted with caution because of multiple limitations in the available data”

FDA recommendations:

Aug 7th
FDA recommends to:

1. When making treatment recommendations, and as part of the informed consent process, consider that there may be an increased rate of long-term mortality in pts treated with PCB and PES.

2. Discuss the risks and benefits of all available PAD treatment options with your pts. For many pts, alternative treatment options to PCB and PES provide a more favorable benefit-risk profile based on currently available information.

3. For individual pts judged to be at particularly high risk for restenosis and repeat fem-pop interventions, clinicians may determine that the benefits of using a paclitaxel-coated device outweigh the risk of late mortality.

4. In discussing treatment options, physicians should explore their pts' expectations, concerns and treatment preferences.

FDA proposed solutions:

1. Don’t use PCB and PES because “alternative treatment options provide a more favorable benefit-risk profile”

2. If you really want to use them, explain to the patient that you are a potential serial killer and, “exploring pts' expectations, concerns and treatment preferences”, try to understand if the patient wants to die potentially earlier or not
There is increased risk of death following application of PCB and PES in the fem-pop artery

TRUE!
There is a clear signal of PTX toxicity!
I should stop to use PTX coated devices

FALSE!
PTX is safe and I can continue to use it!

I am not a statistician!
1° Methodological errors in the meta-analysis

- Unmeasured crossovers and re-interventions, unknown additional PTX exposure
- Pts lost to FU were not accounted for in this meta-analysis. Significant higher FU visit compliance in PTA vs DCB arm → higher FU compliance significantly correlates with higher survival likely due to more frequent and better medical care
- Death types not trending towards any specific cluster
- Causation effect neither found nor hypothesized
<table>
<thead>
<tr>
<th>Level</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°</td>
<td>Methodological errors in the meta-analysis</td>
</tr>
<tr>
<td>2°</td>
<td>No signal present in randomized trials of paclitaxel device use in other vessel beds</td>
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</table>

**FALSE!**

PTX is safe and I can continue to use it!
Coronary Arteriovenous Dialysis access

BTK arteries

Mortality After Pacemaker Use in Dialysis Access: A Systematic Review and Meta-Analysis

Krystal Dinh, BMed, MTrauma
Sharath C. V. Paravastu, MBBS
Shannon D. Thomas, BSc Med
Michael H. Bennett, MBBS, FRACP
Andrew Holden, MBChB, FRACP
and Ramon L. Varcoe, MBBS

IN.PACT DEEP Study: Survival through 5 years

Log-rank p-value = 0.727
Hazard Ratio DCB vs PTA 0.94 [0.65, 1.37]

Survival

Renal arteries

Cook Medical Renal Paclitaxel-eluting Stent: Survival Through 5 years

BMS
n=39
Died=5
KM=15.2%

Paclitaxel Renal Stent
n=81
Died=10
KM=14.1%

p=0.98
Methodological errors in the meta-analysis

No signal present in randomized trials of paclitaxel device use in other vessel beds

Large well-conducted observational studies demonstrate no mortality signal

FALSE!

PTX is safe and I can continue to use it!
Within 2,185 subjects
No mortality signal was confirmed by rigorous methodology on pure RCTs as well as on Registry and combined datasets.

For specific adjustments and methodologies, see the cited publications.
Within 2,185 subjects
Vascular Quality Initiative (VQI)
Bertges D, SVS 2019

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Hazard Ratio (P value)</th>
<th>95% CI</th>
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<tr>
<td>4,880</td>
<td>0.87 (0.12)</td>
<td>0.73, 1.04</td>
</tr>
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Large Observational Studies of Drug vs. Non-Drug
4,880 to 150,000+ subjects

VQI\(^5\)
Medicare Inpatient\(^6\)
OPTUM\(^7\)
Medicare DES\(^8\)
Medicare Inpatient and Outpatient\(^9\)

Subjects
- Follow-up: 4 to 5 years, Up to 5 years, Median 4 years
- N=863, N=971, N=1,055, N=2,185

Mean 509 days, Median 389 days, Median 763 days, Median 2 years, Median 799 days

2. FDA Analysis, pre vital status.
3. FDA Analysis, post vital status.

For specific adjustments and methodologies, see the cited publications.
Secemsky EA et al. JAMA Medicare Beneficiary Data

16,560 pts

Association of Survival With Femoropopliteal Artery Revascularization With Drug-Coated Devices

Adjusted HR 0.97; 95% CI, 0.91-1.04; P = 0.43

Log rank P = 0.07

Hazard Ratio (HR; subject level)
Risk Ratio (RR; study level)

Large Observational Studies of Drug vs. Non-Drug
4,880 to 150,000+ subjects

Optum 7
Medicare
Inpatient 6
Medicare
DES 8
Inpatient and Outpatient 9

N=16,560
N=20,536
N=51,456
N=152,473

Median 389 days
Median 763 days
Median 2 years
Median 799 days

For specific adjustments and methodologies, see the cited publications

5. Medicare Analysis, post vital status.
7. Optum Analysis, post vital status.

OPTUM (Medicare Advantage and commercial payors) - Yeh RW, presented at FDA General Issues Panel June 20, 2019.

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<td>20,536</td>
<td>1.09 (0.11)</td>
<td>0.98, 1.22</td>
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### Observational Studies of Drug vs. Non-Drug
4,880 to 150,000+ subjects

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<tr>
<th>Hazard Ratio (HR; subject level)</th>
<th>Risk Ratio (RR; study level)</th>
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<tbody>
<tr>
<td>0.97</td>
<td>1.09</td>
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<tr>
<td>0.98</td>
<td>0.94</td>
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</tbody>
</table>

### Pooled RCT Analyses
Within 2,185 subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Follow-up</th>
<th>N=865</th>
<th>N=971</th>
<th>N=1,055</th>
<th>N=2,185</th>
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<td>Up to 5 years</td>
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<tr>
<td></td>
<td>Median 4 years</td>
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<td></td>
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</table>

2. FDA Analysis, pre vital status.
3. FDA Analysis, post vital status.

For specific adjustments and methodologies, see the cited publications.

Secemsky EA et al. JACC
Medicare data: 51,456 pts

2. FDA Analysis, post vital status.
3. FDA Analysis, pre vital status.

For specific adjustments and methodologies, see the cited publications.
Secemsky EA, presented at FDA General Issues Panel June 19, 2019 - Medicare fee-for-service inpatient and outpatient claims

152,473 pts

Results
Total Cohort: Unweighted and Weighted Results

- Median follow-up 799 days (IQR 528-1,121 days); longest follow-up 1,573 days

<table>
<thead>
<tr>
<th></th>
<th>Total, Unweighted</th>
<th>Total, Weighted</th>
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<tbody>
<tr>
<td>Log-rank P &lt; 0.001</td>
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<tr>
<td>HR 0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI 0.82, 0.85</td>
<td>47.6%</td>
<td>46.1%</td>
</tr>
<tr>
<td></td>
<td>43.1%</td>
<td>44.7%</td>
</tr>
</tbody>
</table>

For specific adjustments and methodologies, see the cited publications

Secemsky EA, presented at FDA General Issues Panel June 19, 2019 - Medicare fee-for-service inpatient and outpatient claims

152,473 pts

Results
Device Type: Weighted Results

DCB: 23.9% (N=36,410); PTA: 37.2% (N=56,720)

DES: 16.5% (N=25,097); BMS: 22.5% (N=34,246)

DCB vs PTA
Log-rank P<0.001
Adjusted HR 0.93; 95%CI 0.91, 0.95

Cumulative incidence of Death

Days from Index Procedure

47.3%
45.8%

DES vs BMS
Log-rank P=0.03
Adjusted HR 0.97; 95%CI 0.94, 1.00

Cumulative incidence of Death

Days from Index Procedure

44.3%
43.9%

For specific adjustments and methodologies, see the cited publications.

Secemsky EA, presented at FDA General Issues Panel June 19, 2019 - Medicare fee-for-service inpatient and outpatient claims

152,473 pts

### Results

**PAD Severity: Weighted Results**

<table>
<thead>
<tr>
<th>Category</th>
<th>Rate (%)</th>
<th>(N=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CLI</td>
<td>61.3%</td>
<td>93,432</td>
</tr>
<tr>
<td>CLI</td>
<td>38.7%</td>
<td>59,041</td>
</tr>
</tbody>
</table>

#### Non-CLI

- Log-rank P<0.001
- Adjusted HR 0.94; 95%CI 0.92, 0.96

#### CLI

- Log-rank P<0.001
- Adjusted HR 0.94; 95%CI 0.92, 0.97

### Medicare Inpatient and Outpatient

- N=51,456
- N=152,473

- Median 2 years
- Median 799 days

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For specific adjustments and methodologies, see the cited publications

Secemsky EA, presented at FDA General Issues Panel June 19, 2019 - Medicare fee-for-service inpatient and outpatient claims

152,473 pts

Results

Low-Risk Population: Weighted Results

- Median follow-up 969 days (IQR 691-1,251 days); longest follow-up 1,573 days
- DCB: 26.2% (N=3,963), DES: 18.9% (N=2,861), BMS: 23.2% (N=3,503), PTA: 31.7% (N=4,791)

Log-rank P=0.004
Adjusted HR 0.87; 95% CI 0.79, 0.95
Pooled RCT Analyses Within 2,185 subjects

Subjects

Real world analyses of samples sized 2 orders of magnitude higher than pooled RCT analyses seem to refute the presence of a mortality signal associated with the use of PTX-coated devices to treat fem-pop PAD was present.

Pooled RCT Analyses Within 2,185 subjects

VQI Medicare Inpatient OPTUM Medicare DES Medicare Inpatient and Outpatient

N=4,880 N=16,560 N=20,536 N=51,456 N=152,473

Methodological errors in the meta-analysis

No signal present in randomized trials of paclitaxel device use in other vessel beds

Large well-conducted observational studies demonstrate no mortality signal

Collectively, we believe Katsanos’s article represents nothing more than a statistical association with multiple explanations for the findings.....

... at the present time we believe that the undisputed benefit of DES and DCB outweigh their theoretical and uncertain risk.
TRUE!
There is a clear signal of PTX toxicity!
I should stop to use PTX coated devices

Clearly there is an increased mortality signal seen in pts that have been treated with PTX coated devices.

However, it is not known ........ whether this is due to a statistical aberration or a PTX effect. Logic would dictate that it is the former since cancer pts receiving 10 times the PTX dose do not show the effect, and there is no plausible biological mechanism to explain why PTX causes the observed mortality signal.

Even so, there are still ethical and medicolegal implications to continued use of these otherwise beneficial devices in pts.
TRUE!
There is a clear signal of PTX toxicity!
I should stop to use PTX coated devices

So what should we ... do until the clear origin and causality of the mortality signal is known?

If a pt has tolerable IC that can be adequately managed by diminished activity and reassurance, that pt **should not be treated** with a PTX coated device.

If on the other hand, the pt cannot walk more than a few steps or has CLI with rest pain or gangrene, it is appropriate to take substantial treatment risks. The risks of using a PTX coated device and avoiding a redo procedure are much less than those of performing a complex bypass procedure and are easily justifiable, especially in pts with vascular comorbidities who probably have limited life spans anyhow.
There is increased risk of all-cause death up to 5 years following application of PCB and PES in the fem-pop artery.

PTX 14.7%

versus

No-PTX 8.1%

Modified from Secemsky EA, presented at FDA General Issues Panel June 19, 2019 - Medicare fee-for-service inpatient and outpatient claims
There is increased risk of death following application of PCB and PES in the fem-pop artery.

**TRUE!**
If you believe that the PTX “bomb” is true, continue to use PTX devices in CLI pts!

**FALSE!**
If you believe that the PTX “bomb” is false, continue to use PTX devices in every pt!
PTX increases risk of death and amputation in BTK-CLI: NEW breaking News

- 8 RCTs, 1,420 CLI patients
- 1-year death + major Amp: 13.7% (DCB) vs. 9.4% (PTA), \( p=0.008 \)

Multiple enduring questions

- Key confounders:
  1. CLI risk profiles / co-morbidities (high competitive mortality risk)
  2. Therapy (extravascular care)

- Under-powering / Type I error
- Incomplete dataset from non published data
- Same limitations of previous meta-analysis, further amplified within a much more complex population
- Ignoring all learnings from last year critical review of first meta-analysis
In a recent presentation (VEITHsymposium 2019) comparing POBA vs DCB in 1290 patients treated in the last 10 years, with 90% suffering from CLI, no difference in mortality at any time of the follow-up to 6 years was noticed once groups were matched by propensity score analysis.

**Major amputation in CLI patients depends on the patency (foot perfusion) and on wound care.** The studies reported in the meta-analysis have different protocol design and this may explain the difference in the results.

The data of the meta-analysis are incomplete for the ACOART BTK study, which ended the 12-month follow-up in January 2020. A mortality of 7% in the DCB arm and 4% in the POBA arm is reported in the metaanalysis, while the final 12-month data report a mortality of 7.7% in DCB vs 13.2% in POBA patients. Adjusting the meta-analysis with the correct data, the hazard ratio for death reported may change significantly.
My first case using a Stellarex balloon
Stellarex 2.5 x 80 mm: same trackability of an uncoated balloon
Stellarex 2.5 x 80 mm 14 atm
I will continue to use DCBs in every patient!
Vincenzo Foppa, 1462
“The miracle of the salvaged foot”
Cappella Portinari, S. Eustorgio Church
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